Indian College of Radiation Oncology (ICRO)
Association of Radiation Oncologists of India (AROI)

Biological Therapies in Cancer Treatment: Updates & New Directions

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BIOLOGICAL THERAPY

A type of treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in the laboratory.

In cancer, biological therapies:

1. stimulate or suppress the immune system
2. attack specific cancer cells
3. lessen certain side effects caused by some cancer treatments.

Also called biological response modifier therapy, biotherapy, and BRM therapy.

NIH NATIONAL CANCER INSTITUTE

Types of Biological Therapies

1. Monoclonal Antibodies
2. Cancer Vaccines
3. Immune Checkpoint Inhibitors
4. Adoptive Cell Transfer
5. Oncolytic Virus Therapy
6. Cytokine Therapies
7. Targeted Therapy

HISTORY

- The first biologic therapy, taka-diastase, was discovered by Dr. Jokichi Takamine, a Japanese chemist, in 1894.

Diastase is a digestive enzyme whose name comes from the term “diastase,” which means “enzyme,” and “Taka,” which means “best” or “excellent” in Greek and which is also the first half or Dr. Takamine’s name.

In 1894, Takamine was granted the first patent on a microbial enzyme in the United States.

- The discovery and introduction of insulin in 1921 by Banting and Best (1922), is another early biologic therapy.

D.E. Salazar, G. Gormley Modern drug discovery and development Cts-Clin. Transl. Sci. (2017), pp. 719-743

Monoclonal Antibodies

- **1796:** Dr. Edward Jenner pioneered **indirect antibody therapy** by inoculating individuals with pustular fluid from smallpox lesions to induce immunity.

- **1975:** Drs. Kohler and Milstein developed the **hybridoma technique**, fusing myeloma cells with splenic B lymphocytes (both murine in origin).

- Significance: This breakthrough enabled the mass production of monoclonal antibodies (mAbs) with high specificity and consistent quality, revolutionizing targeted therapy.

Evolution of Monoclonal Antibodies:

- **Murine Antibodies**: Initially derived from mice, but triggered human anti-murine antibody (HAMA) responses, leading to immune reactions and limited long-term use.
- **HAMA Effects**: Development of IgE antibodies, increasing the risk of anaphylactic reactions upon repeated administration.
- **Chimeric Antibodies**: Engineered by replacing murine Fc regions with human Fc regions to reduce immunogenicity.
  - Examples: Infliximab, Rituximab
- **Humanized Antibodies**: Further refinement by embedding murine binding sites (protein loops) into human immunoglobulins for better tolerance and efficacy.
  - Examples: Daclizumab, Trastuzumab

Recombinant DNA Technology: Enabled the development of fully human mAbs, such as adalimumab.

Nomenclature Based on Origin:

- -omab → Murine (e.g., Tositumomab)
- -ximab → Chimeric (e.g., Rituximab)
- -zumab → Humanized (e.g., Trastuzumab)
- -umab → Fully Human (e.g., Adalimumab)

Mechanism of Action (MOA):

- Direct cell toxicity (e.g., complement-dependent cytotoxicity)
- Immune-mediated toxicity (e.g., antibody-dependent cellular cytotoxicity)
- Vascular disruption (e.g., inhibiting angiogenesis)
- Immune modulation (e.g., checkpoint inhibition)

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Cancer Vaccines

Definition: Cancer vaccines either treat existing cancer (therapeutic vaccines) or prevent cancer development(preventive vaccines).

- Therapeutic Cancer Vaccines: Also called tumor antigen vaccines, some are autologous, made from the patient's own tumor cells, providing a personalized approach.
- Immunosurveillance Theory: Suggests that cancerous cells frequently arise but are eliminated by the immune system before forming tumors. Cancer develops when immune evasion occurs.

Viral & Bacterial Causes of Cancer:

- Virus-related cancers: HPV → Cervical cancer; Hepatitis B → Liver cancer
- Bacteria-related cancers: *H. pylori* → Stomach cancer
- Preventive vaccines: HPV and Hepatitis B vaccines reduce cancer risk.

Types of Cancer Vaccines

- **Cell-Based Vaccines**
  - Utilize whole tumor cells or tumor cell lysates.
  - Autologous (from the patient) offers a broad range of antigens but is costly and requires sufficient tumor cells.
  - Allogeneic (from established cancer cell lines) can overcome limitations but has shown limited efficacy.
  - Example: Canvaxin (melanoma vaccine) failed in Phase III trials.

Dendritic Cell-Based Vaccines

This strategy uses the patient's own dendritic cells, loaded with tumor antigens, to directly activate T-cells—bypassing the need for native antigen-presenting cells.

The most well-known example, Sipuleucel-T (Provenge), extended survival by only four months.

A key challenge with dendritic cell vaccines is ensuring effective migration to lymph nodes for optimal T-cell interaction.

Peptide-Based Cancer Vaccines

These vaccines use cancer-specific peptides (epitopes) and often require an adjuvant, like GM-CSF, to boost immune response. Examples include Her2 peptides (GP2, NeuVax). However, this approach is limited by MHC restriction, requiring patient-specific MHC profiling.

A solution to this limitation is using synthetic long peptides or purified proteins, which antigen-presenting cells (APCs) process into epitopes, making the vaccine more broadly applicable.

Gene-Based Cancer Vaccines

- These vaccines use DNA or RNA to encode tumor-related genes, which are then expressed in antigen-presenting cells (APCs) and processed into immune-stimulating epitopes. A key challenge is efficient gene delivery. One promising candidate, mRNA-4157/V940, is exploring mRNA-based approaches for cancer treatment.

Approved Vaccines:

- Oncophage (Russia, 2008) – Approved for kidney cancer
- Sipuleucel-T (Provenge) (USA, 2010) – Approved for metastatic hormone-refractory prostate cancer
- CimaVax-EGF (Cuba, 2011) – Undergoing phase II trials for further applications in USA
- BCG Vaccine (USA, 1990) – Approved for early-stage bladder cancer

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IMMUNE CHECKPOINT INHIBITORS

- Immune checkpoints are a normal part of the immune system.

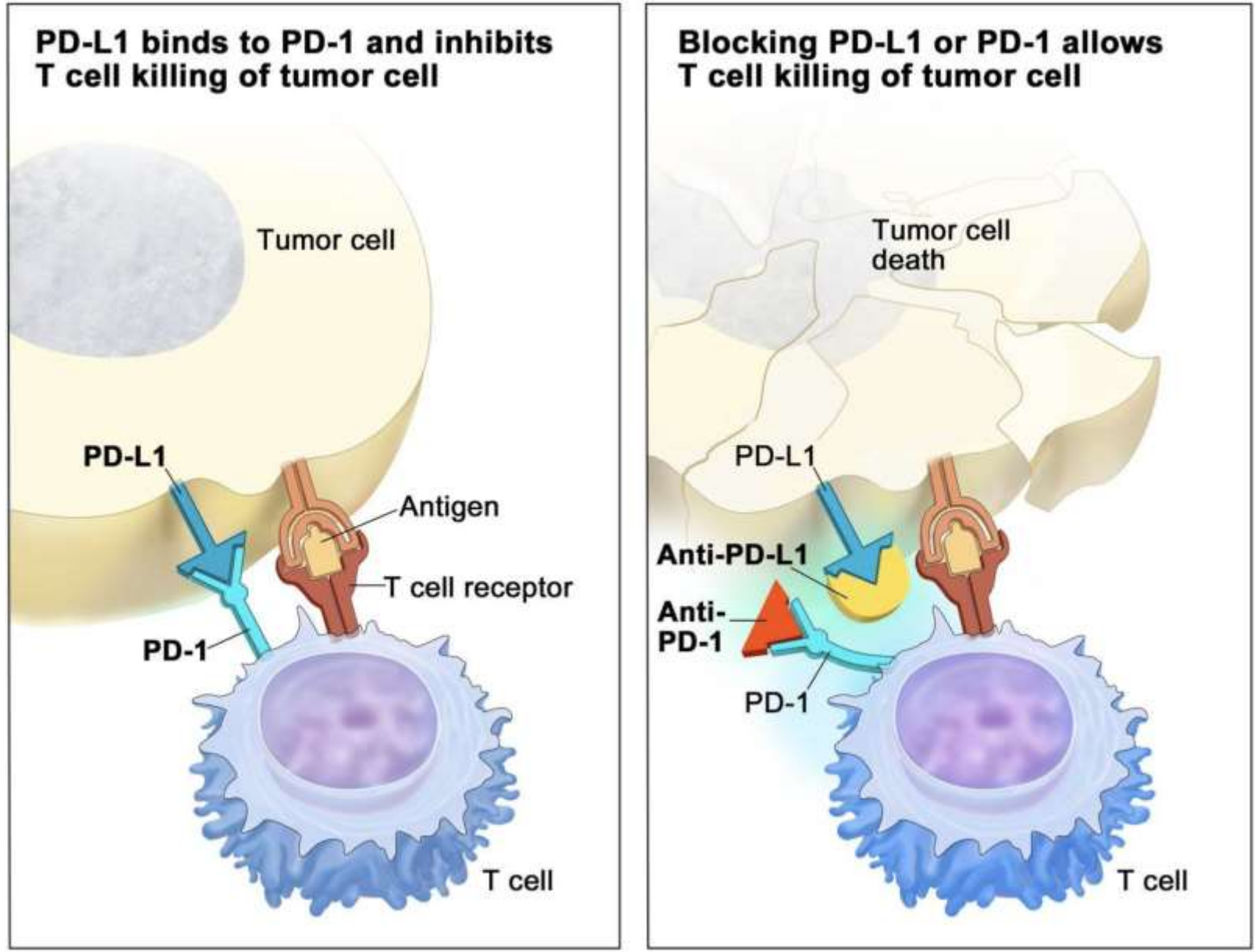
- Immune checkpoints help regulate the immune system by preventing excessive T-cell activation. They work when checkpoint proteins on T cells bind to partner proteins on other cells, including tumor cells, sending an "off" signal that stops the immune response.

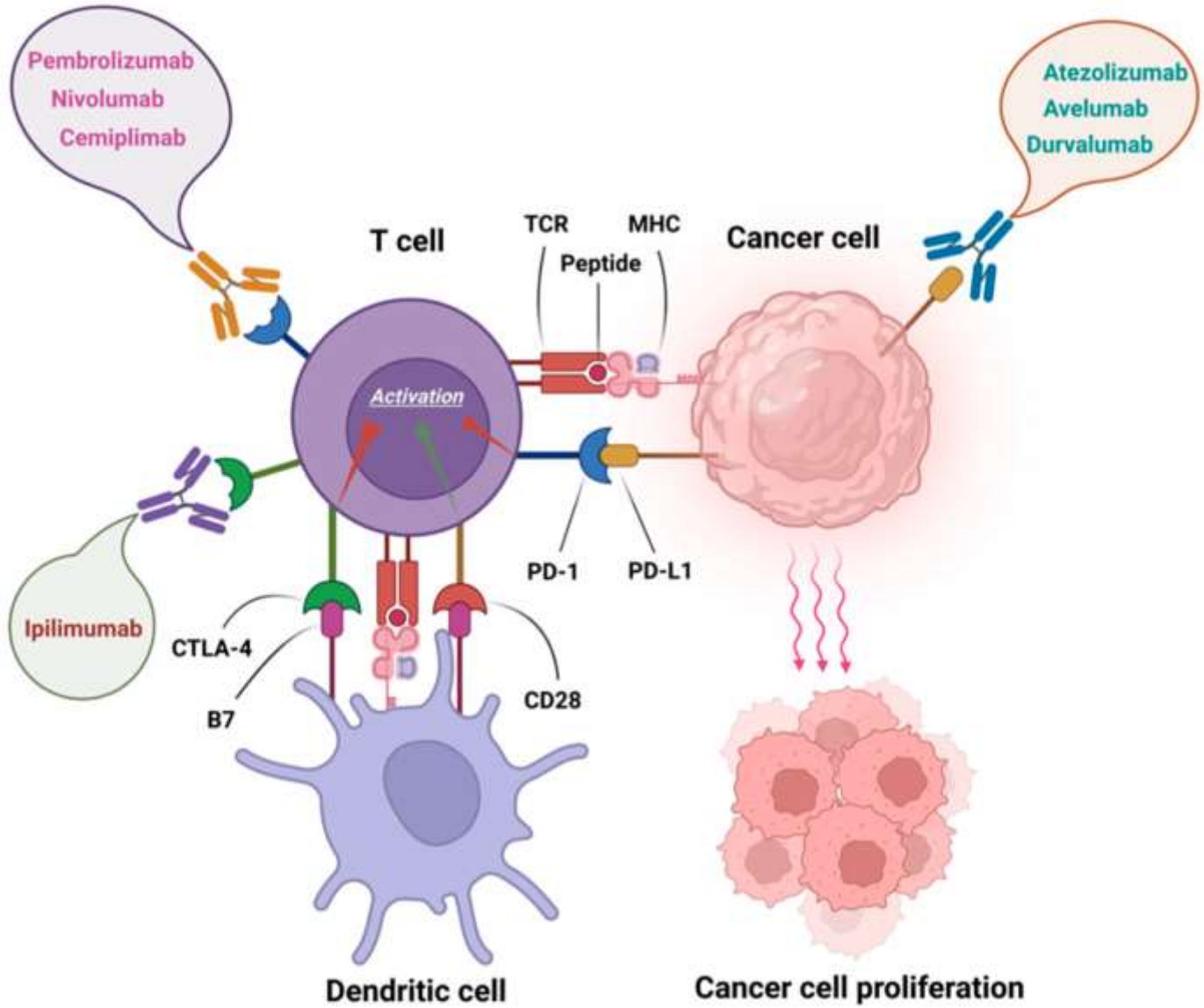
- Checkpoint inhibitors are immunotherapy drugs that block this interaction, preventing the "off" signal and allowing T cells to attack cancer cells.

PD-1 and CTLA-4

PD-1 and CTLA-4 are inhibitory receptors on T cells that help regulate immune responses. However, tumor cells exploit these checkpoints to suppress T-cell activity, leading to immune tolerance and T-cell exhaustion.

Immune checkpoint inhibitors (ICIs)—such as anti-CTLA-4, anti-PD-1, and anti-PD-L1—block these inhibitory signals, reactivating T cells to attack tumor cells.


PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti-PD-L1
Anti-PD-1
PD-1
T cell


Pembrolizumab
Nivolumab
Cemiplimab
Atezolizumab
Avelumab
Durvalumab
T cell
TCR
MHC
Peptide
Cancer cell
Activation
Ipilimumab
CTLA-4
B7
CD28
PD-1
PD-L1
Dendritic cell
Cancer cell proliferation

Only 20–40% of patients respond to immune checkpoint inhibitors, emphasizing the need for predictive biomarkers. Factors influencing immunotherapy outcomes include:

- Tumor mutational burden (TMB)
- PD-L1 expression
- Microbiome
- Hypoxia & Interferon-γ levels
- Extracellular matrix (ECM)
- Tumor microenvironment (TME)

Insights from Clinical Studies:

- Patients with advanced hepatocellular carcinoma (HCC) have shown poor overall survival (OS) with novel treatments.
- Combination therapy of ICIs + tyrosine kinase inhibitors (TKIs) provided better outcomes than sunitinib monotherapy in metastatic renal cell carcinoma (mRCC).

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Adoptive Cell Transfer

A form of immunotherapy where T cells are extracted from the patient, expanded in the lab, and reintroduced to fight cancer.

Types of ACT:

- Chimeric Antigen Receptor (CAR) T-Cell Therapy
  - T cells are genetically modified to express a CAR that enhances their ability to recognize and attack cancer cells.
  - Effective in hematologic malignancies (e.g., B-cell leukemia, lymphoma).
- Tumor-Infiltrating Lymphocyte (TIL) Therapy
  - T cells naturally present in the tumor microenvironment are extracted, expanded, and reinfused.
  - Shows promise in solid tumors like melanoma.

Also known as T-cell transfer therapy or cellular adoptive immunotherapy.

- Tumor-infiltrating lymphocyte (TIL) therapy, engineered T cell receptor (TCR)-T cell therapy, and CAR-T cell therapy are the three primary ACTs.

- Among them, CAR-T therapy has received marketing approval and achieved considerable success in the treatment of hematological malignancies.

- The use of autologous TILs in ACT to elicit tumor regression in patients with metastatic malignant melanoma was first demonstrated by Rosenberg et al. in 2002

Tumor-infiltrating lymphocyte (TIL)

TILs are a group of lymphocytes that infiltrate into tumors, including T cells, NK cells, and others. These lymphocytes can recognize and destroy tumor cells as well as mobilize bystander immune cells to help combat the tumor.

The lack of sufficient TILs and the dysfunction produced by the unfavorable tumor microenvironment (TME) frequently prevent TILs from performing their anti-tumor activity.

TIL therapy, a method based on TIL isolation, ex vivo expansion, and subsequent re-implantation.

TIL therapy advantages for treating solid tumors:

(1) TILs can circumvent the problem of heterogeneity of solid tumors because they are composed of T cells that target multiple antigens in cancer cells.

(2) TILs, which are isolated from tumors, can easily infiltrate tumors because they already possess an appropriate chemokine receptor system.

(3) As TILs are derived from patients, the reinfused TILs typically do not cause noticeable adverse effects.

TIL therapy has yet to be approved by the US FDA owing to its numerous limitations:

1) Not all tumor tissues are suitable for isolating active lymphocytes that target tumor cells.
2) Because a large number of lymphocytes are needed for TIL therapy, some patients with rapidly progressing diseases cannot wait for the isolated TIL to grow in vitro, which typically takes 2 months.
3) TILs become exhausted from prolonged in vitro expansion, showing poor cytotoxicity and persistence.
4) Because TIL therapy is entirely customized and cannot yield a universal product, it is challenging to maintain consistent TIL quality.

T cell receptor (TCR)-T cell therapy

- TCR-T cell therapy is a process wherein normal T cells are transduced with antigen-specific TCR α and β chains to produce tumor-specific T cells, which are then amplified and reinfused into the body to specifically kill tumor cells.

- Rosenberg et al.,- genetically modified lymphocytes expressing multiple TCRs against specific tumor antigens (TCR-engineered T cells) have promising therapeutic potential for metastatic melanoma.

TCR-T cells advantages:

(1) With a complete TCR structure, TCR-T cells can fully mediate TCR signaling and recruit all costimulatory molecules and thus show potent anti-tumor activity.

(2) TCR activation is dependent on the antigen presented by MHC. Because MHC can present endogenous overexpressed antigens and neoantigens as well as foreign viral proteins and is unaffected by the subcellular localization of such antigens, TCR-T cell therapy is effective against a large target antigen pool.

(3) Only a very small amount of target antigen is required to activate TCR.

Limitations:

- On-target off-tumor toxicity- Targeting inappropriate antigens with T cells can lead to serious and sometimes fatal toxicities.

- Poor persistence- TCR-T cells frequently fail to mount a durable immune response in patients.

- Expression and correct pairing of engineered TCR- affected by the competition between exogenous and endogenous TCR.

- Unable to handle the constraints of the TME- In solid tumors, the expression of CXCL9 and other chemokines that recruit T cells is decreased, whereas the concentration of inhibitory cells and molecules is increased, creating an inhibitory immune milieu that substantially inhibits TCR-T cell activity

CAR-T

T cells can recognize antigens as peptides presented by MHC via TCR; however, tumor cells frequently downregulate the expression of MHC-I molecules to evade T cell recognition.

CAR was developed to circumvent this constraint.

CAR-T cell therapy like TCR- T cell therapy uses gene transduction techniques (retrovirus, lentivirus, non-viral vector, etc.) to confer T cells the ability to precisely attack tumors by introducing antigen-specific CAR molecules into them.

Because of differences in their structural makeup and antigen-recognition mechanisms, CAR and TCR function differently.

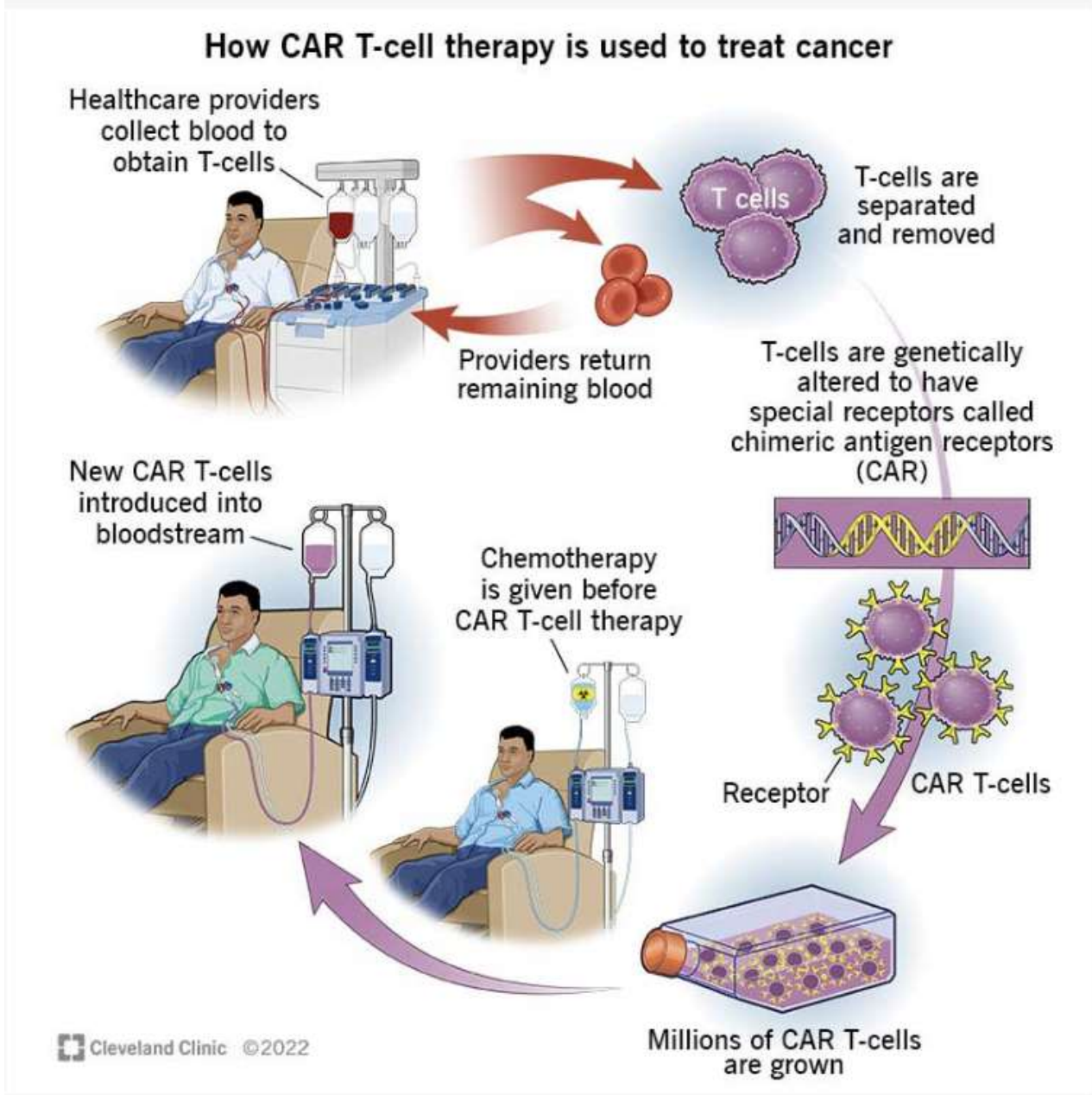
CAR-T cell therapies are a cutting-edge option for patients with relapsed or treatment-resistant blood cancers, especially large B-cell lymphomas and multiple myeloma (MM).

So far, **6 CAR-T therapies** have been **FDA-approved**:

- Axicabtagene ciloleucel
- Brexucabtagene autoleucel
- Idecabtagene vicleucel *(MM)*
- Lisocabtagene maraleucel
- Tisagenlecleucel
- Ciltacabtagene autoleucel *(MM)*

Approved indications include:

- B-cell Acute Lymphoblastic Leukemia (ALL)
- Diffuse Large B-cell Lymphoma (DLBCL)
- Follicular Lymphoma
- High-grade B-cell Lymphoma
- Mantle Cell Lymphoma
- Multiple Myeloma
- Primary Mediastinal Large B-cell Lymphoma


How CAR T-cell therapy is used to treat cancer
Healthcare providers collect blood to obtain T-cells
T cells
T-cells are separated and removed
Providers return remaining blood
T-cells are genetically altered to have special receptors called chimeric antigen receptors (CAR)
New CAR T-cells introduced into bloodstream
Chemotherapy is given before CAR T-cell therapy
Receptor
CAR T-cells
Millions of CAR T-cells are grown
Cleveland Clinic ©2022

Limitation:

1. **Target Selection** – CAR-T cells can only recognize surface antigens, unlike TCR-T cells, which detect intracellular targets via MHC. This limits available targets and increases the risk of on-target/off-tumor toxicity as many targets are also found in normal tissues.

2. **Infiltration** – CAR-T cells struggle to penetrate solid tumors due to chemotactic defects and barriers created by the dense extracellular matrix (ECM).

3. **Exhaustion** – Repeated stimulation by tumor cells, prolonged in vitro expansion, and an immunosuppressive tumor microenvironment (TME) lead to CAR-T cell exhaustion and loss of function.

4. Antigen Escape – Tumor cells with low antigen density can evade CAR-T therapy, leading to relapse.

5. Safety Concerns – Besides on-target/off-tumor effects, CAR-T therapy is associated with serious toxicities, including cytokine release syndrome (CRS) and neurotoxicity (NT).

6. Graft-versus-Host Disease (GvHD) & Host-versus-Graft Rejection (HvGR) – Allogeneic CAR-T cells can help overcome T-cell shortages, but MHC mismatches can trigger GvHD (potentially fatal) or HvGR, leading to CAR-T cell elimination.

Comparison of CAR-T and CAR-NK Cell Therapies

- **CAR-T Cells**
  - Kill tumor cells only through CAR-dependent mechanisms.
  - Ineffective against tumor cells with low or absent tumor-associated antigen (TAA) expression, leading to tumor escape.
  - Susceptible to PD-L1/PD-L2-mediated immunosuppression, which weakens their anti-tumor response.
- **CAR-NK Cells**
  - Kill tumor cells via both CAR-mediated and natural cytotoxicity mechanisms.
  - Can eliminate TAA-negative or low-expressing tumor cells, reducing the risk of tumor escape.
  - Can also attack tumor cells through antibody-dependent cellular cytotoxicity (ADCC) and recruit other immune cells.
  - Less sensitive to PD-L1/PD-L2-mediated suppression, making them potentially more effective in immunosuppressive environments.

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Oncolytic Virus Therapy

The idea of using viruses to treat cancer dates back to the early 20th century. Reports from 1904 and 1912 described patients with leukemia and cervical cancer experiencing tumor regression after viral infections.

Oncolytic Viruses (OVs) are engineered or naturally occurring viruses that:

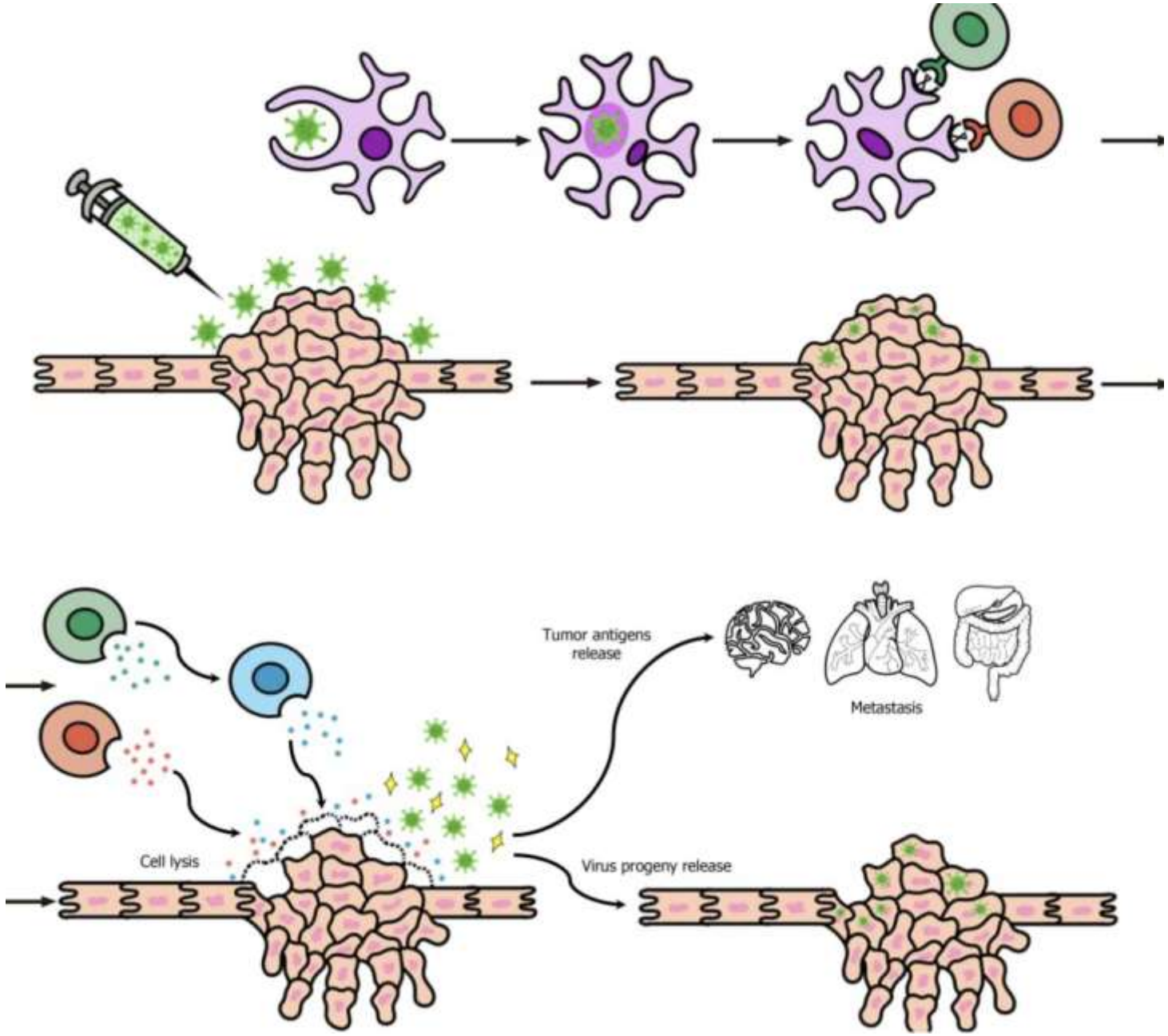
- Infect and destroy tumor cells while sparing normal cells.
- Target tumors naturally or through genetic modification to enhance specificity.
- Help slow tumor growth and stimulate an anti-tumor immune response.

Targeting Mechanism:

- OVs selectively infect tumor cells by recognizing specific molecular targets, such as:
- Nuclear transcription factors: hTERT (human telomerase reverse transcriptase), PSA, COX-2, osteocalcin.
- Surface markers: PSMA, folate receptor, CD20, EGFR, Her2/neu—proteins commonly produced by tumor cells.

Delivery Methods:

- Local administration (greater viral control, fewer side effects):
  - Intratumoral (direct injection into tumors)
  - Intraperitoneal (for abdominal tumors)
  - Intrathecal (for brain/spinal tumors)
  - Subcutaneous
- Intravenous (IV) administration – Used for treating distant metastases.


Tumor antigens release
Metastasis
Cell lysis
Virus progeny release

ONCOLYTIC VIRUSES

- Adenovirus
- Protoparvovirus
- Vaccinia virus
- Reovirus
- Herpes simplex virus type I

CLINICAL USES

- **Pancreatic Cancer** – Reolysin® (a reovirus) is in Phase II clinical trials.
- **Melanoma** – T-VEC was the first FDA-approved oncolytic virus for melanoma treatment.
- **Breast Cancer** – T-VEC (approved for melanoma) has been clinically tested in breast cancer.
- **Pelareorep (Reolysin®)**, an RNA virus, has also been studied.
- **Other Cancers Under Investigation:** Liver Cancer, Glioblastoma, Prostate Cancer, Colorectal Cancer

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Cytokine Therapies

Cytokines are small proteins (5–25 kDa) primarily produced by immune cells in response to infection, inflammation, or injury. They are also secreted by fibroblasts, epithelial, endothelial, and stromal cells.

Functions:

- Mediating cell-cell communication and immune responses.
- Regulating cell differentiation & proliferation (can either promote or inhibit).
- Influencing the tumor microenvironment (TME) by coordinating immune and inflammatory responses.

Saenz *et al*., 2008, Goldstein and Laszlo, 1988; Dranoff, 2004, Floros and Tarhini, 2015

Certain cytokines have been explored as cancer immunotherapies due to their ability to:

- Modulate the immune response against cancer cells.
- Directly exhibit anti-cancer effects, such as inhibiting tumor growth and inducing apoptosis.

Historical Perspective:

- Cytokine therapy dates back to the 1970s.
- Interferon-alpha (IFN-α) and Interleukin-2 (IL-2) were the first cytokines used in cancer treatment.

INTERLEUKIN-2 (IL-2)

- IL-2 is a key cytokine in cancer immunotherapy.
- Produced mainly by activated CD4+ and CD8+ T cells, but also by naïve T cells, NK cells, and dendritic cells.

Mechanism of Action

- IL-2 binds to a three-subunit receptor complex (IL-2Rα (CD25), IL-2Rβ (CD122), and common-γ chain (CD132)).
- These receptors are primarily found on activated T cells, regulatory T cells, mature dendritic cells, and B cells.
- Low IL-2 levels promote CD4+ T cell differentiation into follicular helper or central memory T cells.
- High IL-2 levels stimulate CD8+ T cell and NK cell expansion & activation, enhancing anti-tumor responses.

Clinical Approvals: 1992 – FDA approval for metastatic renal cell carcinoma. 1998 – FDA approval for metastatic melanoma.

(Cheng *et al.*, 2002; Wang *et al.*, 2009; Skrombolas and Frelinger, 2014

IFN-alpha

First FDA-approved anticancer cytokine (1986) for hairy cell leukemia.

Later used for chronic myeloid leukemia (CML) and solid tumors like melanoma and renal cancer.

Pegylation (attachment of polyethylene glycol) was introduced to increase its half-life and enhance efficacy in clinical use.

Other Interferons in Cancer Therapy

- IFN-Gamma (Type II IFN)
  - Activates the JAK/STAT signaling pathway, similar to Type I IFNs.
  - Inhibits tumor cell proliferation, induces apoptosis, and arrests the cell cycle.
- IFN-Beta
  - Also developed as an anticancer cytokine.

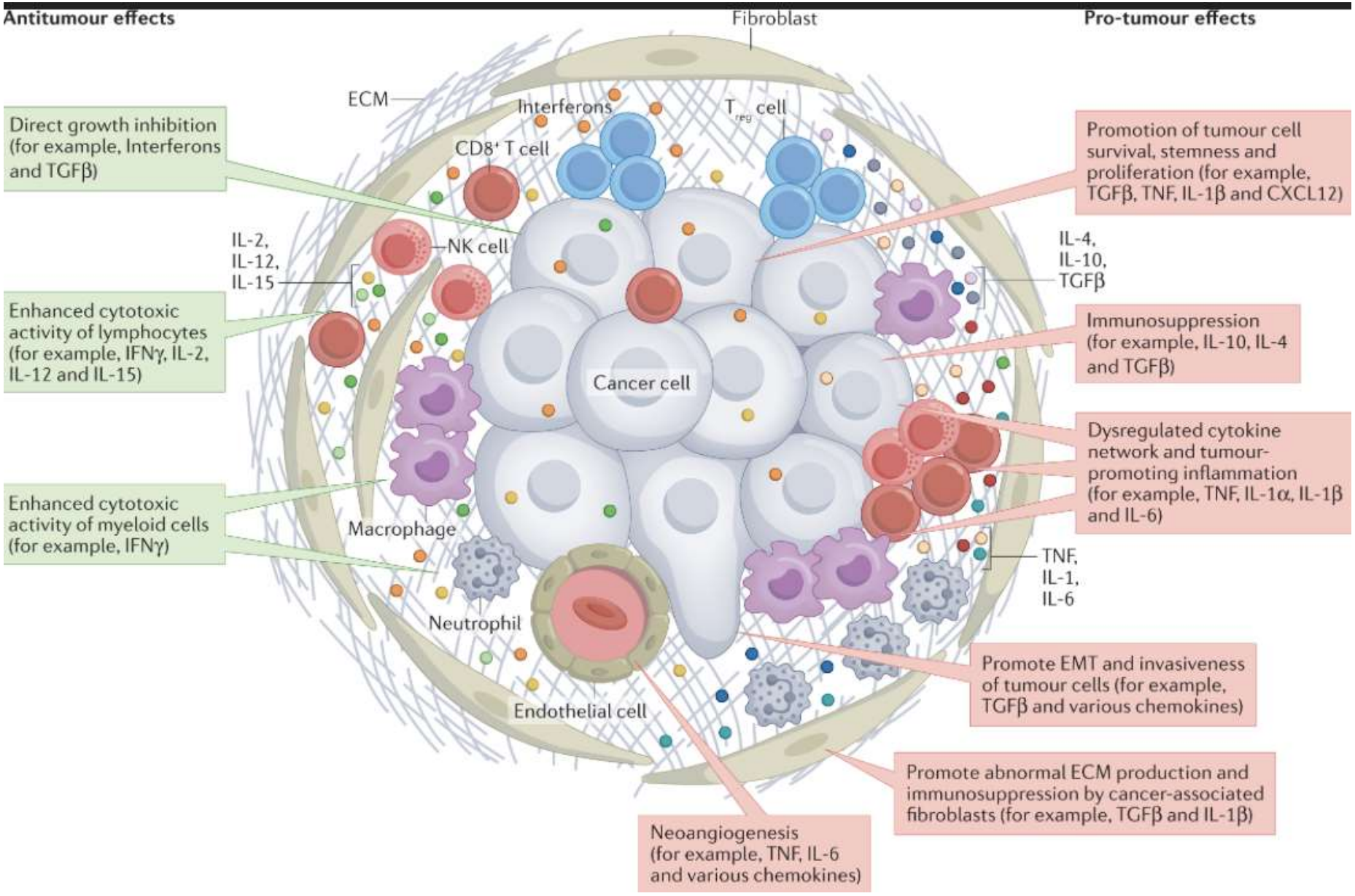
GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM- CSF)

M-CSF is a cytokine that stimulates the production of myeloid cells, including neutrophils, monocytes, macrophages, and dendritic cells in the tumor microenvironment.

Clinical trials for GM-CSF increased steadily until 2010, but have since declined.

Role in Cancer Therapy

- Similar anti-tumor effects as other cytokines.
- 80% of GM-CSF-related clinical trials used natural cytokines.
- 20% explored cell-based gene therapies incorporating GM-CSF.


Antitumour effects
Pro-tumour effects
Fibroblast
ECM
Interferons
T_{reg} cell
CD8⁺ T cell
NK cell
IL-2,
IL-12,
IL-15
Cancer cell
Macrophage
Neutrophil
Endothelial cell
IL-4,
IL-10,
TGFβ
TNF,
IL-1,
IL-6
Direct growth inhibition (for example, Interferons and TGFβ)
Enhanced cytotoxic activity of lymphocytes (for example, IFNγ, IL-2, IL-12 and IL-15)
Enhanced cytotoxic activity of myeloid cells (for example, IFNγ)
Promotion of tumour cell survival, stemness and proliferation (for example, TGFβ, TNF, IL-1β and CXCL12)
Immunosuppression (for example, IL-10, IL-4 and TGFβ)
Dysregulated cytokine network and tumour-promoting inflammation (for example, TNF, IL-1α, IL-1β and IL-6)
Promote EMT and invasiveness of tumour cells (for example, TGFβ and various chemokines)
Promote abnormal ECM production and immunosuppression by cancer-associated fibroblasts (for example, TGFβ and IL-1β)
Neoangiogenesis (for example, TNF, IL-6 and various chemokines)

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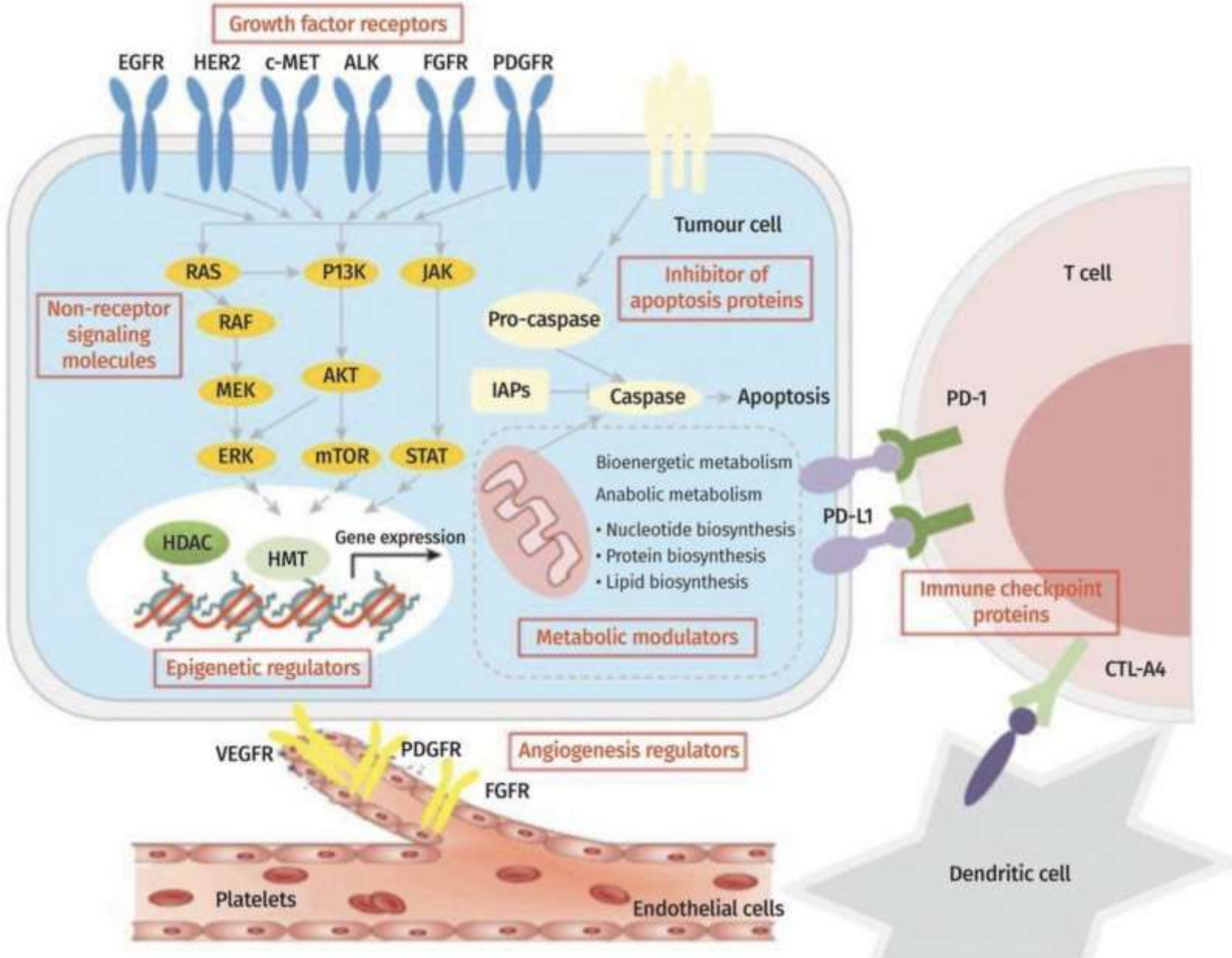
Targeted Therapy

Targeted therapy focuses on specific genetic mutations and abnormal proteins that drive cancer growth.

Unlike chemotherapy, which affects all rapidly dividing cells, targeted therapy acts only on cancer-related proteins.

Mechanism of Action

- Targets cell surface antigens, growth factors, receptors, or signaling pathways involved in:
  - Cell cycle regulation
  - Cell death (apoptosis)
  - Metastasis
  - Angiogenesis (blood vessel formation for tumors)


Growth factor receptors
EGFR
HER2
c-MET
ALK
FGFR
PDGFR
Tumour cell
RAS
P13K
JAK
RAF
MEK
AKT
ERK
mTOR
STAT
Non-receptor signaling molecules
Pro-caspase
Inhibitor of apoptosis proteins
IAPs
Caspase
Apoptosis
Bioenergetic metabolism
Anabolic metabolism
• Nucleotide biosynthesis
• Protein biosynthesis
• Lipid biosynthesis
Metabolic modulators
HDAC
HMT
Gene expression
Epigenetic regulators
T cell
PD-1
PD-L1
Immune checkpoint proteins
CTL-A4
Dendritic cell
VEGFR
PDGFR
FGFR
Angiogenesis regulators
Platelets
Endothelial cells

Types of Targeted Therapies

Most targeted therapies fall into two main categories:

- Monoclonal antibodies (mAbs)
- Small-molecule drugs

However, they can also be classified into: Hormone therapies, Signal transduction inhibitors, Gene expression modulators, Apoptosis inducers, Angiogenesis inhibitors, Immunotherapies, Toxin delivery molecules.

Mechanism of Action

- Blocking signals that promote cancer cell growth.
- Disrupting cell cycle regulation to slow tumor progression.
- Inducing cell death (apoptosis) to eliminate cancer cells.

Types of targeted therapy

The two most common types of targeted therapy are:

- **Monoclonal Antibodies (mAbs)**
  - Target specific proteins on the cancer cell surface or in the tumor microenvironment.
  - Cannot enter the cell due to their large size.
  - Work by:
    - Blocking growth signals that promote cancer cell proliferation.
    - Inhibiting angiogenesis (formation of new blood vessels that feed tumors).

- Monoclonal antibodies can be linked to a toxic substance, such as standard chemotherapy or radionuclides,to deliver the therapy to the cancer cells.

- Brentuximab vedotin7 (used in treating Hodgkin lymphoma and some other lymphomas) is an example of a monoclonal antibody–drug conjugate.

- Clinical pearl: The names of monoclonal antibodies often end in -mab (eg, rituximab, bevacizumab, trastuzumab, pertuzumab, panitumumab).

- Monoclonal antibodies (mAbs) can be linked to toxic substances, such as:
  - Chemotherapy drugs
  - Radionuclides (radiation-emitting molecules)

- This approach delivers therapy directly to cancer cells, increasing effectiveness while reducing damage to healthy cells.

- Example: Antibody-Drug Conjugate (ADC)

- Brentuximab vedotin – used for Hodgkin lymphoma and certain other lymphomas.

- Clinical Pearl- The names of monoclonal antibodies typically end in "-mab” *(e.g., rituximab, bevacizumab, trastuzumab, pertuzumab, panitumumab).*

HER2-Targeted Therapy in Cancer Treatment

- HER2 (ERBB2) overexpression occurs in HER2-positive breast and gastric cancers.
- Monoclonal antibodies used for HER2-positive breast cancer:
  - Trastuzumab and Pertuzumab – target different regions of HER2 to block cancer growth.
  - Trastuzumab emtansine – an antibody-drug conjugate that delivers a cytotoxic drug directly to HER2-positive tumor cells.

Treatment for HER2-Negative Breast Cancer

- Cyclin-dependent kinase (CDK) 4/6 inhibitors (e.g., palbociclib, ribociclib)
  - Used for hormone receptor-positive, HER2-negative breast cancers.
  - Help block cell cycle progression, slowing tumor growth.

Targeted Therapies for Specific Cancer Types

1. DNA Repair Inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, niraparib)

- Block DNA repair enzymes, making cancer cells more vulnerable to damage.
- Used in ovarian cancer treatment.
- Olaparib is also used for BRCA mutation–positive breast cancer.

2. EGFR-Targeted Therapy for Non–Small Cell Lung Cancer (NSCLC)

- EGFR mutations drive rapid tumor growth.
- EGFR tyrosine kinase inhibitors (TKIs) (e.g., osimertinib, gefitinib, erlotinib)
  - Block EGFR signaling, slowing cancer progression.

3. ALK-Targeted Therapy for NSCLC

- Anaplastic lymphoma kinase (ALK) mutations promote tumor survival.
- ALK inhibitors (e.g., crizotinib)
  - Specifically target ALK-mutant lung cancers.

1. Colorectal Cancer Treatment

- Bevacizumab (monoclonal antibody)
  - Binds to vascular endothelial growth factor (VEGF), preventing the formation of tumor blood vessels (angiogenesis).
- Panitumumab (monoclonal antibody)
  - Targets epidermal growth factor receptor (EGFR) to inhibit cancer growth.
  - KRAS mutations may reduce its effectiveness, so mutation testing is recommended before treatment.

2. Melanoma Treatment

- BRAF mutations occur in ~50% of melanomas, leading to uncontrolled cell growth.
- BRAF inhibitors (e.g., vemurafenib, dabrafenib)
  - Target mutant BRAF proteins to slow cancer progression.
- Mitogen-activated protein kinase (MEK) inhibitors (e.g., trametinib)
  - Can be used alone or in combination with BRAF inhibitors for better results.

Side-effects

1. EGFR Inhibitors

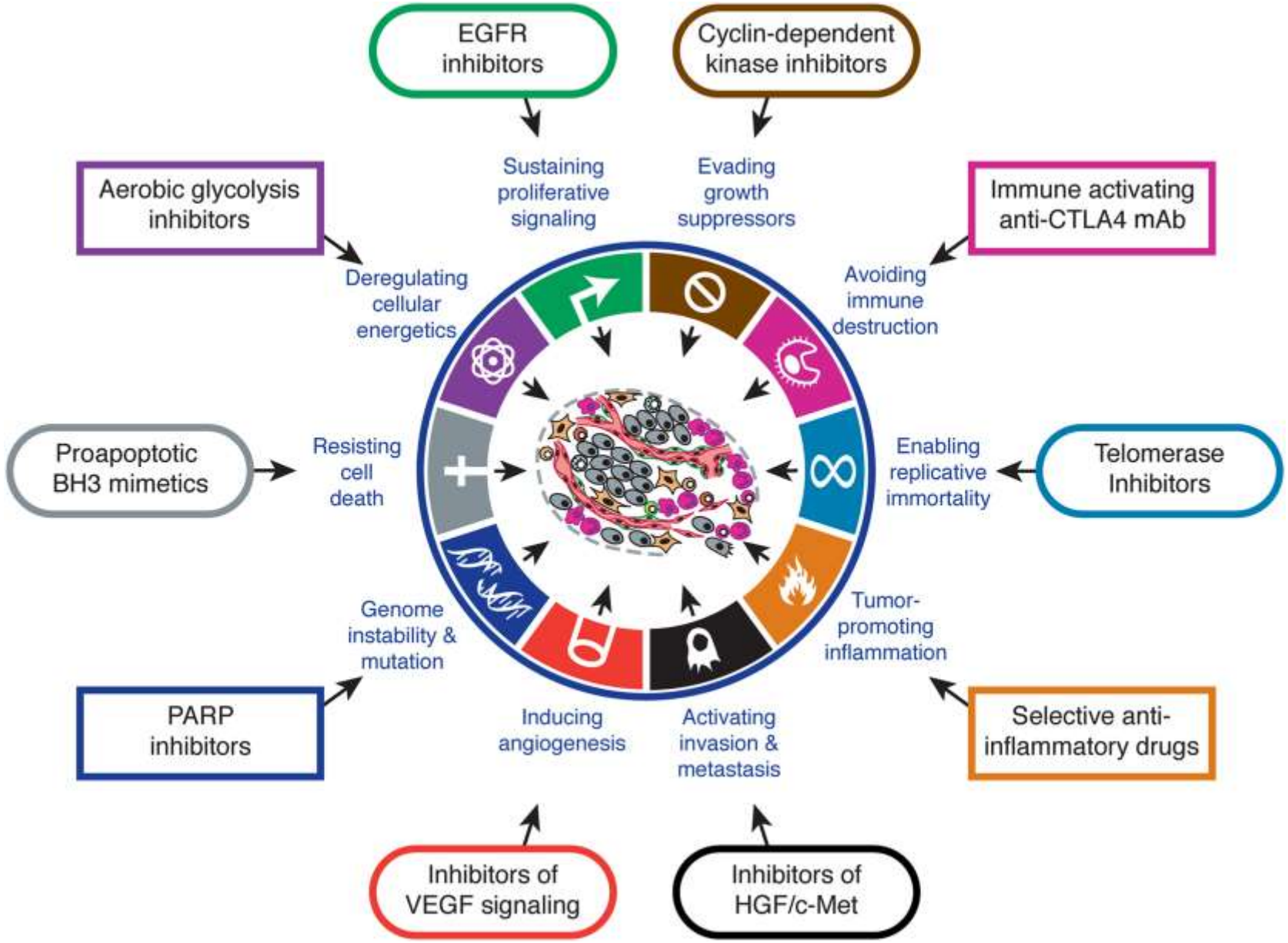
- Acneiform rash
- Nail changes
- Hair discoloration
- Dry skin
- Yellow skin discoloration

2. HER2-Targeted Therapy (e.g., Trastuzumab)

- Potential risk: Congestive heart failure

3. VEGF and VEGF Receptor Inhibitors

- Hypertension
- Thromboembolic events (blood clots)
- Impaired wound healing
- Increased risk of bleeding, including tumor-associated hemorrhage


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Take home message

- **Immunotherapy is transforming cancer care**, offering targeted, personalized approaches with durable responses in select malignancies.
- **CAR-T cell therapy** shows remarkable efficacy in hematologic cancers but faces challenges in solid tumors, including tumor heterogeneity and TME barriers.
- **Oncolytic viruses** not only lyse tumor cells directly but also stimulate systemic antitumor immunity—representing a dual-action approach.
- **Cytokines** can enhance immune responses but must be carefully dosed to balance efficacy and toxicity.
- **Targeted immunotherapies** (e.g., checkpoint inhibitors, bispecific antibodies) are effective in several tumor types, especially when guided by biomarkers.
- **Cancer vaccines** are gaining ground with neoantigen-based strategies and personalized designs in clinical development.
- **Combination strategies**, biomarker-driven approaches, and modulation of the tumor microenvironment are key to overcoming resistance.

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THANK YOU